
Keppra *levetiracetam*

Version NCDSv08 JM Exc



Film-coated tablets

Oral solution

Concentrate for injectable solution for infusion

Administration

Oral

Intravenous

Composition

KEPPRA 500 mg Film-coated Tablets

Each film-coated tablet contains: Levetiracetam 500 mg, sodium croscarmellose, opadry 85F32004, colloidal anhydrous silica, macrogol 6000, magnesium stearate.

KEPPRA 1000 mg Film-coated tablets

Each film coated tablet contains: Levetiracetam 1000 mg, sodium croscarmellose, opadry 85F18422, colloidal anhydrous silica, macrogol 6000, magnesium stearate.

KEPPRA 100 mg/mL Oral solution

Each mL contains: Levetiracetam 100 mg, maltitol Lycasin, glycerol 85 %, acesulfame potassium, methyl parahydroxybenzoate, ammonium glycyrrhizate, sodium citrate, propyl parahydroxybenzoate, grape flavor, citric acid monohydrate, purified water.

Each 100 mL contain: Levetiracetam 10 g, maltitol Lycasin, glycerol 85 %, acesulfame potassium, methyl parahydroxybenzoate, ammonium glycyrrhizate, sodium citrate, propyl parahydroxybenzoate, grape flavor, citric acid monohydrate, purified water.

KEPPRA 500 mg/5 mL Concentrate for Injectable Solution for Infusion

Each vial (5 mL) contains: Levetiracetam 500 mg, sodium chloride, sodium acetate, glacial acetic acid, water for injection q.s.

Not all strengths and/or presentations are available in all markets.

Pharmacological Properties

ATC Code

N03AX14.

Pharmacotherapeutic Group

Antiepileptics; Other Antiepileptics.

The active substance, Levetiracetam, is a pyrrolidone derivative (S-enantiomer of α -ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.

The mechanism of action of Levetiracetam still remains to be fully elucidated. *In vitro* and *in vivo* experiments suggest that Levetiracetam does not alter basic cell characteristics and normal neurotransmission.

In vitro studies show that Levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing the release of Ca^{2+} from intraneuronal stores. In addition it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and β -carbolines. Furthermore, Levetiracetam has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. This binding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analogs show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between Levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.

Therapeutic Indications

Levetiracetam is Indicated as Monotherapy in the Treatment of:

- Partial onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam is Indicated as Adjunctive Therapy in the Treatment of:

- Partial onset seizures with or without secondary generalization in adults, adolescents, children from 4 years of age with epilepsy.
- Myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.
- Primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Contraindications

Levetiracetam is contraindicated in:

- Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients.

Special Warnings and Special Precautions for Use

Discontinuation

If Levetiracetam has to be discontinued it is recommended to withdraw it gradually (e.g. in adults and adolescents weighing more than 50 Kg: 500 mg decreases twice daily every two to four weeks; children and adolescents weighing less than 50 Kg: dose decrease should not exceed 10 mg/Kg twice daily every two weeks).

Renal or Hepatic Impairment

The administration of Levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

Acute Kidney Injury

The use of Levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

Blood cell Counts

Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with Levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (*see Undesirable Effects*).

Depression and/or Suicidal Ideation

Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including Levetiracetam). A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known.

Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge.

Paediatric Population

The tablet formulation is not adapted for use in infants and children under the age of 6 years.

Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

Excipients

Oral Solution

Levetiracetam 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

It also includes maltitol liquid; patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

It contains glycerol which may cause, stomach upset and diarrhoea.

Solution for Infusion

This medicinal product contains 2.5 mmol (or 57 mg) sodium per maximum single dose (0.83 mmol (or 19 mg) per vial). It should be taken into consideration by patients on a controlled sodium diet.

Interaction with Other Medicinal Products and Other Forms of Interaction

Antiepileptic Medicinal Products

Pre-marketing data from clinical studies conducted in adults indicate that Levetiracetam did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Levetiracetam.

As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/Kg/day Levetiracetam.

A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered Levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher Levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required.

Probenecid

Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of Levetiracetam. Nevertheless, the concentration of this metabolite remains low.

Methotrexate

Concomitant administration of Levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and Levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs.

Oral Contraceptives, Digoxin and Warfarin

Levetiracetam 1000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not

modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of Levetiracetam.

Laxatives

There have been isolated reports of decreased Levetiracetam efficacy when the osmotic laxative macrogol has been concomitantly administered with oral Levetiracetam. Therefore, macrogol should not be taken orally for one hour before and for one hour after taking Levetiracetam.

Food and Alcohol

The extent of absorption of Levetiracetam was not altered by food, but the rate of absorption was slightly reduced.

No data on the interaction of Levetiracetam with alcohol are available.

Pregnancy and Lactation

Fertility

No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown.

Pregnancy

Levetiracetam is not recommended during pregnancy and in women of childbearing potential not using contraception unless clearly necessary.

Post-marketing data from several prospective pregnancy registries have documented outcomes in over 1000 women exposed to Levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity.

Physiological changes during pregnancy may affect Levetiracetam concentration. Decrease in Levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60 % of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with Levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the fetus.

Lactation

Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

However, if Levetiracetam treatment is needed during breastfeeding, the benefit/ risk of the treatment should be weighed considering the importance of breastfeeding.

Effects on Ability to Drive and Use Machines

Levetiracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, e.g. driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected.

Undesirable Effects

Clinical Trial Data and Post-Marketing Data

Summary of the Safety Profile

The undesirable effects profile presented below is based on the analysis of pooled placebo-controlled clinical trials with all indications studied, with a total of 3416 patients treated with Levetiracetam. These data are supplemented with the use of Levetiracetam in corresponding open-label extension studies, as well as post-marketing experience. The most frequently reported undesirable effect were nasopharyngitis, somnolence, headache, fatigue and dizziness. The safety profile of Levetiracetam is generally similar across age groups (adult and paediatric patients) and across the approved epilepsy indications.

Undesirable effects are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

| | |
|-------------|--|
| Very common | ≥1/10 |
| Common | ≥1/100 to <1/10 |
| Uncommon | ≥1/1 000 to <1/100 |
| Rare | ≥1/10 000 to <1/1 000 |
| Very rare | 1/10 000 |
| Not known | (cannot be estimated from the available data). |

Infections and Infestations

| | |
|-------------|------------------|
| Very common | Nasopharyngitis. |
| Rare | Infection. |

Blood and Lymphatic System Disorders

| | |
|----------|---|
| Uncommon | Thrombocytopenia, leucopenia. |
| Rare | Pancytopenia, neutropenia, agranulocytosis. |

Immune System Disorders

| | |
|------|---|
| Rare | Drug reaction with eosinophilia and systemic symptoms (DRESS), hypersensitivity (including angioedema and anaphylaxis). |
|------|---|

Metabolism and Nutrition Disorders

| | |
|----------|------------------------------------|
| Common | Anorexia. |
| Uncommon | Weight decreased, weight increase. |
| Rare | Hyponatraemia. |

Psychiatric Disorders

| | |
|----------|---|
| Common | Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability. |
| Uncommon | Suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusional state, panic attack, affect lability/ mood swings, agitation. |

| | |
|------|---|
| Rare | Completed suicide, personality disorder, abnormal thinking. |
|------|---|

Nervous System Disorders

| | |
|-------------|---|
| Very common | Somnolence, headache |
| Common | Seizure, balance disorder, dizziness, lethargy, tremor |
| Uncommon | Amnesia, memory impairment, abnormal coordination/ataxia, paraesthesia, disturbance in attention. |
| Rare | Choreoathetosis, dyskinesia, hyperkinesia |

Eye Disorders

| | |
|----------|---------------------------|
| Uncommon | Diplopia, vision blurred. |
|----------|---------------------------|

Ear and Labyrinth Disorders

| | |
|--------|----------|
| Common | Vertigo. |
|--------|----------|

Respiratory, Thoracic and Mediastinal Disorders

| | |
|--------|--------|
| Common | Cough. |
|--------|--------|

Gastrointestinal Disorders

| | |
|--------|---|
| Common | Abdominal pain, diarrhoea, dyspepsia, vomiting, nausea. |
| Rare: | Pancreatitis. |

Hepatobiliary Disorders

| | |
|----------|--------------------------------|
| Uncommon | Abnormal liver function tests. |
| Rare | Hepatic failure, hepatitis. |

Renal and Urinary Disorders

| | |
|------|----------------------|
| Rare | Acute kidney injury. |
|------|----------------------|

Skin and Subcutaneous Tissue Disorders

| | |
|----------|--|
| Common | Rash. |
| Uncommon | Alopecia, eczema, pruritus, |
| Rare | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme. |

Musculoskeletal and Connective Tissue Disorders

| | |
|----------|--|
| Uncommon | Muscular weakness, myalgia. |
| Rare | Rhabdomyolysis and blood creatine phosphokinase increased* |

General Disorders and Administration Site Conditions

| | |
|--------|-------------------|
| Common | Asthenia/fatigue. |
|--------|-------------------|

Injury, Poisoning and Procedural Complications

| | |
|---|---------|
| Uncommon | Injury. |
| * Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients. | |

Cases of encephalopathy have been rarely observed after Levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Description of Selected Undesirable Effects

The risk of anorexia is higher when Levetiracetam is co-administered with topiramate.

In several cases of alopecia, recovery was observed when Levetiracetam was discontinued.

Bone marrow suppression was identified in some of the cases of pancytopenia.

Paediatric Population

In patients aged 4-16 years, a total of 645 patients have been treated with Levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with Levetiracetam in placebo-controlled studies. These data are supplemented with the post-marketing experience of the use of Levetiracetam.

The undesirable effect profile of Levetiracetam is generally similar across age groups and across the approved epilepsy indications. Safety results in paediatric patients in placebo-controlled clinical studies were consistent with the safety profile of Levetiracetam in adults except for behavioral and psychiatric undesirable effects which were more common in children than in adults. In children and adolescents aged 4 to 16 years, vomiting (very common, 11.2 %), agitation (common, 3.4 %), mood swings (common, 2.1 %), affect lability (common, 1.7 %), aggression (common, 8.2 %), abnormal behaviour (common, 5.6 %), and lethargy (common, 3.9 %) were reported more frequently than in other age ranges or in the overall safety profile.

A double-blind, placebo-controlled paediatric safety study with a non-inferiority design has assessed the cognitive and neuropsychological effects of Levetiracetam in children 4 to 16 years of age with partial onset seizures. It was concluded that Levetiracetam was not different (non inferior) from placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Results related to behavioral and emotional functioning indicated a worsening in Levetiracetam treated patients on aggressive behaviour as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist). However subjects, who took Levetiracetam in the long term open label follow-up study, did not experience a worsening, on average, in their behavioral and emotional functioning; in particular measures of aggressive behaviour were not worse than baseline.

Incompatibilities

None.

Posology and Method of Administration

Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained.

Film-Coated Tablets

The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The daily dose is administered in two equally divided doses.

Oral Solution

The oral solution may be diluted in a glass of water or baby’s bottle and may be taken with or without food. The daily dose is administered in two equally divided doses.

Concentrate for Solution for Infusion

Levetiracetam concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 mL of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (see Instructions for Use and Handling).

There is no experience with administration of intravenous Levetiracetam for longer period than 4 days.

Levetiracetam concentrate is an alternative for patients (adults and children from 4 years of age) when oral administration is temporarily not feasible.

Adults

Monotherapy

Adults and Adolescents from 16 Years of Age

The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.

Add-on Therapy

Adults (≥ 18 years) and Adolescents (12 to 17 years) Weighing 50 Kg or More

The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment.

Depending upon the clinical response and tolerability, the daily dose can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks.

Children

The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose.

The tablet formulation is not adapted for use in infants and children under the age of 6 years. Levetiracetam oral solution is the preferred formulation for use in this population. In addition, the available dose strengths of the tablets are not appropriate for initial treatment in children weighing less than 25 Kg, for patients unable to swallow tablets or for the administration of doses below 250 mg. In all of the above cases Levetiracetam oral solution should be used.

The safety and efficacy of Levetiracetam concentrate for solution for infusion in infants and children less than 4 years have not been established.

Monotherapy

The safety and efficacy of Levetiracetam in children and adolescents below 16 years as monotherapy treatment have not been established.

There are no data available.

Add-on Therapy

Add-on Therapy for Children (4 to 11 years) and Adolescents (12 to 17 years) Weighing Less than 50 Kg

Levetiracetam oral solution is the preferred formulation for use in children under the age of 6 years.

For children 6 years and above, Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.

The initial therapeutic dose is 10 mg/Kg twice daily.

Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/Kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/Kg twice daily every two weeks. The lowest effective dose should be used.

Dose in children 50 Kg or greater is the same as in adults.

Dose recommendations for children from 4 years of age and adolescents

| Weight | Starting dose 10 mg/Kg twice daily | Maximum dose 30 mg/Kg twice daily |
|---------------------------|---------------------------------------|--------------------------------------|
| 10 Kg ⁽¹⁾ | 100 mg (1 mL) twice daily | 300 mg (3 mL) twice daily |
| 15 Kg ⁽¹⁾ | 150 mg (1.5 mL) twice daily | 450 mg (4.5 mL) twice daily |
| 20 Kg ⁽¹⁾ | 200 mg (2 mL) twice daily | 600 mg (6 mL) twice daily |
| 25 Kg | 250 mg twice daily | 750 mg twice daily |
| From 50 Kg ⁽²⁾ | 500 mg twice daily | 1500 mg twice daily |

⁽¹⁾ Children 25 Kg or less should preferably start the treatment with Levetiracetam 100 mg/mL oral solution
⁽²⁾ Dose in children and adolescents 50 Kg or more is the same as in adults

Elderly

Adjustment of the dose is recommended in elderly patients with compromised renal function.

Renal Impairment

The daily dose must be individualized according to renal function (see Special Warnings and Special Precautions for Use).

For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient’s creatinine clearance (CLcr) in mL/min is needed. The CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination, for adults and adolescents weighing 50 Kg or more, using the following formula:

$$CL_{cr} \left(\text{mL/min} \right) = \frac{\left[140 - \text{age} \left(\text{years} \right) \right] \times \text{weight} \left(\text{kg} \right)}{72 \times \text{serum creatinine} \left(\text{mg/dL} \right)} \times 0.85 \left(\text{for women} \right)$$

Then CLcr is adjusted for body surface area (BSA) as follows:

$$CL_{cr} \left(\text{mL/min/1.73m}^2 \right) = \frac{CL_{cr} \left(\text{mL/min} \right)}{BSA \text{ subject} \left(\text{m}^2 \right)} \times 1.73$$

Dosing adjustment for adult and adolescent patients weighing more than 50 Kg with impaired renal function

| Group | Creatinine clearance (mL/min/1.73 m²) | Dosage and frequency |
|---|--|--|
| Normal | >80 | 500 to 1500 mg twice daily |
| Mild | 50 - 79 | 500 to 1000 mg twice daily |
| Moderate | 30 - 49 | 250 to 750 mg twice daily |
| Severe | <30 | 250 to 500 mg twice daily |
| End-stage renal disease patients undergoing dialysis ⁽¹⁾ | - | 500 to 1000 mg once daily ⁽²⁾ |

⁽¹⁾ A 750 mg loading dose is recommended on the first day of treatment with Levetiracetam.
⁽²⁾ Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, Levetiracetam dose needs to be adjusted based on the renal function as Levetiracetam clearance is related to renal function.

This recommendation is based on a study in adult renally impaired patients.

The CLcr in mL/min/1.73 m² may be estimated from serum creatinine (mg/dL) determination using, for young adolescents and children using the following formula (Schwartz formula):

$$CL_{cr} \left(\text{mL/min/1.73m}^2 \right) = \frac{\text{Height} \left(\text{cm} \right) \times \text{ks}}{\text{Srum Creatinine} \left(\text{mg/dL} \right)}$$

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for children from 4 years of age and adolescents patients weighing less than 50 Kg with impaired renal function

| Group | Creatinine clearance (mL/min/1.73 m²) | Dosage and frequency ⁽¹⁾ Children from 4 years of age and adolescents weighing less than 50 Kg |
|--|--|---|
| Normal | >80 | 10 to 30 mg/Kg (0.10 to 0.30 mL/Kg) twice daily |
| Mild | 50 - 79 | 10 to 20 mg/Kg (0.10 to 0.20 mL/Kg) twice daily |
| Moderate | 30 - 49 | 5 to 15 mg/Kg (0.05 to 0.15 mL/Kg) twice daily |
| Severe | <30 | 5 to 10 mg/Kg (0.05 to 0.10 mL/Kg) twice daily |
| End-stage renal disease patients undergoing dialysis | - | 10 to 20 mg/Kg (0.10 to 0.20 mL/Kg) once daily ^{(2) (3)} |

⁽¹⁾ Levetiracetam oral solution should be used for doses under 250 mg, for doses not multiple of 250 mg when dosing recommendation is not achievable by taking multiple tablets and for patients unable to swallow tablets.
⁽²⁾ A 15 mg/Kg (0.15 mL/Kg) loading dose is recommended on the first day of treatment with Levetiracetam.
⁽³⁾ Following dialysis, a 5 to 10 mg/Kg (0.05 to 0.10 mL/Kg) supplemental dose is recommended.

Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 mL/min/1.73 m².

Overdose

Symptoms and Signs

Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses.

Treatment

There is no specific antidote for Levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyzer extraction efficiency is 60 % for Levetiracetam and 74 % for the primary metabolite.

Further management should be as clinically indicated or as recommended by the national poisons center, where available.

Special Precautions for Storage

Do not store above 30°C. Keep out of the reach of children.

Presentations

| | |
|---|------------------------|
| KEPPRA 500 mg Film-coated tablets | Box x 30’s. |
| KEPPRA 1000 mg Film-coated tablets | Box x 30’s. |
| KEPPRA 100 mg/mL Oral solution | Box x bottle x 300 mL. |
| KEPPRA 500 mg/5 mL Concentrate for injectable solution for infusion | Box x 10 vials. |

Not all presentations are available in all markets.

Instructions for use and Handling

Levetiracetam, 100 mg/mL Concentrate for Solution for Infusion

Table presents the recommended preparation and administration of Levetiracetam concentrate to achieve a total daily dose of 500 mg, 1000 mg, 2000 mg, or 3000 mg in two divided doses.

| Dose | Withdrawal Volume | Volume of Diluent | Infusion time | Frequency of administration | Total Daily Dose |
|--------|-------------------------|-------------------------|------------------|--------------------------------|---------------------|
| 250 mg | 2.5 mL (half 5 mL vial) | 100 mL | 15 minutes | Twice daily | 500 mg/day |



| Dose | Withdrawal Volume | Volume of Diluent | Infusion time | Frequency of administration | Total Daily Dose |
|---------|--------------------------|-------------------|---------------|-----------------------------|------------------|
| 500 mg | 5 mL (one 5 mL vial) | 100 mL | 15 minutes | Twice daily | 1000 mg/day |
| 1000 mg | 10 mL (two 5 mL vials) | 100 mL | 15 minutes | Twice daily | 2000 mg/day |
| 1500 mg | 15 mL (three 5 mL vials) | 100 mL | 15 minutes | Twice daily | 3000 mg/day |

This medicinal product is for single use only, any unused solution should be discarded.

This medicinal product must not be mixed with other medicinal products except those mentioned below. Levetiracetam concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15°C - 25°C.

Diluents

- Sodium chloride (0.9 %) injection.
- Lactated Ringer's injection.
- Dextrose 5 % injection.

Medicinal product with particulate matter or discoloration should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Film-coated Tablets

Oral solution

Concentrate for injectable solution for infusion

Packed by

Made by: UCB Pharma S.A., Braine-l'Alleud, Belgium.

Made by: NextPharma S.A.S., Limay, France.

Made by: Patheon Italia S.p.A., Monza, Italy.

Aesica Pharmaceuticals S.R.L., Pianezza, Italy.

Based on

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